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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,590	11/25/2003	Dennis Triglia	VITA1120-1	7574

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,590	TRIGLIA ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-25 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 8-11-06 has been entered. Claims 20-22 and 24 have been amended. Claim 29 has been added. Claims 1-29 are pending. Claims 20-25 and 29 are under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 20-25 remain rejected and the newly added claim 29 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention and is repeated for the reasons set forth in the preceding Official action mailed 5-9-06. Applicants' arguments filed 8-11-06 have been fully considered but they are not persuasive.

Claims 20-22 have been amended to recite cell line deposited as ATCC accession No. CRL-12461 or cells clonally derived from cells deposited as ATCC accession No. CRL-12461. Claim 21 is further amended to read on attaching the bio-artificial liver device to a subject between an artery and vein of the subject, and the cultured cells interact with the blood to provide bio-artificial liver support for the subject. Claim 22 is further amended to read on removing blood-borne toxic solutes entering the device and release of protein and low molecular weight products from the cells into blood exiting said device. Claim 24 has been amended to

recite the compromised liver function is associated with fluminant hepatic failure (FHF). Claim 29 specifies the protein is albumin.

Applicants argue that clinical data and tumor formation should be left to FDA not USPTO and the requirement to meet standards of FDA is not appropriate. Applicants further argue that the specification teaches critical liver functions to be considered, use of polarized aggregates in hollow cartridge, cell density to achieve necessary function and specific disease to be treated. The specification provides prediction of function based on tested and workable materials and designs of prosthetics well known in the art at the time of the invention (amendment, p. 8-9). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-9-06 and the following reasons:

Firstly, claims 21-25 and 29 still read on culturing cells of CRL-12461 or cells clonally derived from CRL-12461 on various type of bio-artificial device made of different materials and designs to treat numerous different liver disorders or diseases in a subject with said device outside or inside said subject. The amended claim 21 must have a use for the cells in a bio-artificial device and such use is to treat a subject having a liver disorder, condition, or compromised liver function in light of the specification. Although the specification teaches critical liver functions to be considered, use of polarized aggregates in hollow cartridge, and cell density to achieve necessary function, however, the specification only provides a prophetic method of treating a subject having a liver disorder by using a bio-artificial device. Whether sufficient claimed cells can be obtained in the bio-artificial liver device inside or outside a subject and whether those claimed cells can provide sufficient liver specific biological activity to treat any liver disorder or disease in said subject were unpredictable at the time of the invention.

The specification fails to provide adequate guidance and evidence for whether any of the claimed cells can be cultured in or on any bio-artificial device to produce sufficient cells in SFM so as to provide sufficient liver specific biological activity for removal of blood-borne toxic solutes and release of protein and low molecular weight products in the blood of a subject having compromised liver function and to treat said subject with said device outside or inside said subject.

Secondly, the safety aspects and tumor formation may be left to FDA, however, the specification must provide sufficient enabling disclosure for the claimed invention but fails to do so. As discussed above, the specification only provides a prophetic method of treating a subject having a liver disorder by using a bio-artificial device. Bioartificial liver (BAL) must provide a number of crucial liver functions including synthesizing many proteins, such as clotting factors, producing bile, regulating carbohydrate, fat and protein metabolism, detoxifying ammonia product and breaking down alcohol and drugs. It is unclear whether the claimed cells can provide those crucial liver functions and whether sufficient cells can be obtained in the bio-artificial liver device to provide therapeutic effect in a subject. The claims read on using the claimed cells for treating a subject having compromised liver function alone. The specification fails to provide adequate guidance and evidence whether the claimed cells are phenotypically stable and can provide sufficient liver specific biological activities without the presence of non-parenchymal liver cells and bile duct epithelial cells for optimal hepatic activity as taught by Strain, and whether sufficient number of claimed cells could be cultured on the BAL to support a patient's failing liver. Further, the specification fails to provide adequate guidance and evidence for how to maintain the hepatocytes cell culture ex vivo and in vivo. Monolayer cultures cannot

optimally maintain hepatocytes, and it is likely that hepatocytes will need to be induced to form cellular aggregates in which they reacquire their polarization. Interactions among the different types of hepatic cell populations are essential for the liver to operate appropriately. Coculture of hepatocytes with nonparenchemal liver cells has been shown to be beneficial. The claims do not recite what kind of bio-artificial liver device would be used. The specification fails to provide adequate guidance and evidence for whether the claimed cells alone would form a monolayer of cells or form cellular aggregates in which type of BAL device, and whether the claimed cells would be able to provide sufficient liver specific biological activities for treating a subject having compromised liver function.

Thirdly, a subject having compromised liver function includes a subject having numerous different liver disease or disorders. Different liver diseases or disorders differ pathologically, morphologically and physiologically, and the mechanisms that result in compromised liver function could vary dramatically in different liver diseases or disorders. The specification fails to provide adequate guidance for the correlation between removal of blood-borne toxic solutes entering the device as well as release of molecules from the cells and the treatment of a subject having compromised liver function. It is unclear what kind of blood-borne toxic solutes should be removed from the blood entering the artificial device and what kind of molecules should be released from the cells into blood exiting said device so as to provide therapeutic effect for treating a subject having a particular liver disorder or compromised liver function.

Lastly, the claims encompass using cells clonally derived from the cells of ATCC accession No. CRL-12461. Cells clonally derived from the cells of ATCC accession No. CRL-12461 could deviate from the parental CRL-12461 cells and could have different biological

activity as compared to the parental CRL-12461. The specification fails to provide evidence for whether cells clonally derived from the cells of ATCC accession No. CRL-12461 have liver specific biological activities and said cells can provide therapeutic effect in treating liver disorder or disease in a subject via the use of a bio-artificial liver device either outside or inside the body of said subject.

In view of the reasons set forth above, claims 20-25 remain rejected and the newly added claim 29 is rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 20 and 21 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Spiering, et al., 1994 (In Vitro Cellular and Developmental Biology Animal, Vol. 30A, No. 3,

Part 2, pp. 106) in view of Price et al., US Patent No. 6,103,529 and is repeated for the reasons set forth in the preceding Official action mailed 5-9-06. Applicants' arguments filed 8-11-06 have been fully considered but they are not persuasive.

Applicants argue that the cited reference do not teach cells clonally derived from cells deposited as ATCC accession No. CRL-12461, and the cited reference teaches away from the present invention because the output of albumin as recited in Spiering is lower than the intrinsic output of albumin observed for the cells as claimed. Therefore, there is no motivation to combine the cited reference and there is no reasonable expectation of success (amendment, p. 10-11). This is not found persuasive because cells clonally derived from cells of CRL-12461 can be different from the cells of CRL-12461 but could be the same as the hepatix C3A cells as taught by Spiering. It would be obvious for one of ordinary skill in the art to use the hepatix C3A cells as taught by Spiering. Table 2 of the instant invention shows various albumin productions (mg/day) at different date of sample, however, there is no 2.2 x 10-8 g of human albumin/day/cell in Table 2. Examiner is confused how the number 2.2 x 10-8 g of human albumin/day/cell is obtained in Table 2. In view of such, claims 20 and 21 remain rejected under 35 U.S.C. 103(a).

Conclusion

No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER